JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

# Mechanism of the Acid-Promoted Intramolecular Schmidt Reaction: Theoretical Assessment of the Importance of Lone Pair−Cation, Cation−π, and Steric Effects in Controlling Regioselectivity

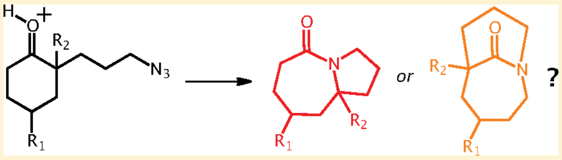
Osvaldo Gutierrez,[†] Jeffrey Aubé,[‡] and Dean J. Tantillo*[,†]

[†]Department of Chemistry, University of California at Davis, Davis, California 95616, United States

[‡]Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045, United States

Supporting Information

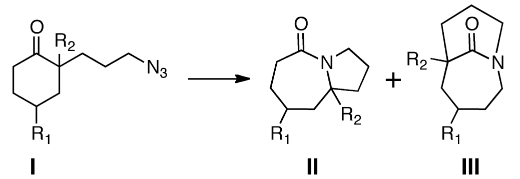
**ABSTRACT:** The mechanism of the acid-catalyzed intramolecular Schmidt reaction of 2-azidopropylcyclohexanones was studied using density functional theory (primarily M06-2X). The reaction was found to proceed through rapid formation of azidohydrin intermediates followed by rate-determining concerted $N_2$-loss/shift of the alkyl group antiperiplanar to the $N_2$ leaving group. For cases where steric, lone pair−cation, and cation−π effects have been invoked previously as regiocontrol elements, the origins and magnitudes of these effects have been examined theoretically.



## INTRODUCTION

The intramolecular Schmidt reaction was reported in 1991 to be an effective and general means of generating fused lactams having different ring sizes and substitution patterns (e.g., Scheme 1).[1,2]

**Scheme 1**



Using this methodology to access *bridged* bicyclic lactams (**III**)[3] as major products proved more challenging but was ultimately shown to be promoted by the positioning of an aryl[4] or thioether[5,6] group at the α-position of the ketone ($R_2$ in Scheme 1), which was proposed to provide selective stabilization to the transition state structure for formation of the bridged system through cation−π[7] or lone pair−cation interactions with the departing $N_2$ group. Herein, we present the results of a theoretical study on the mechanism of the intramolecular Schmidt reaction of 2-azidopropylketones (I) and the factors controlling the competition between the formation of fused (II) and bridged (III) lactam products.[8]

## METHODS

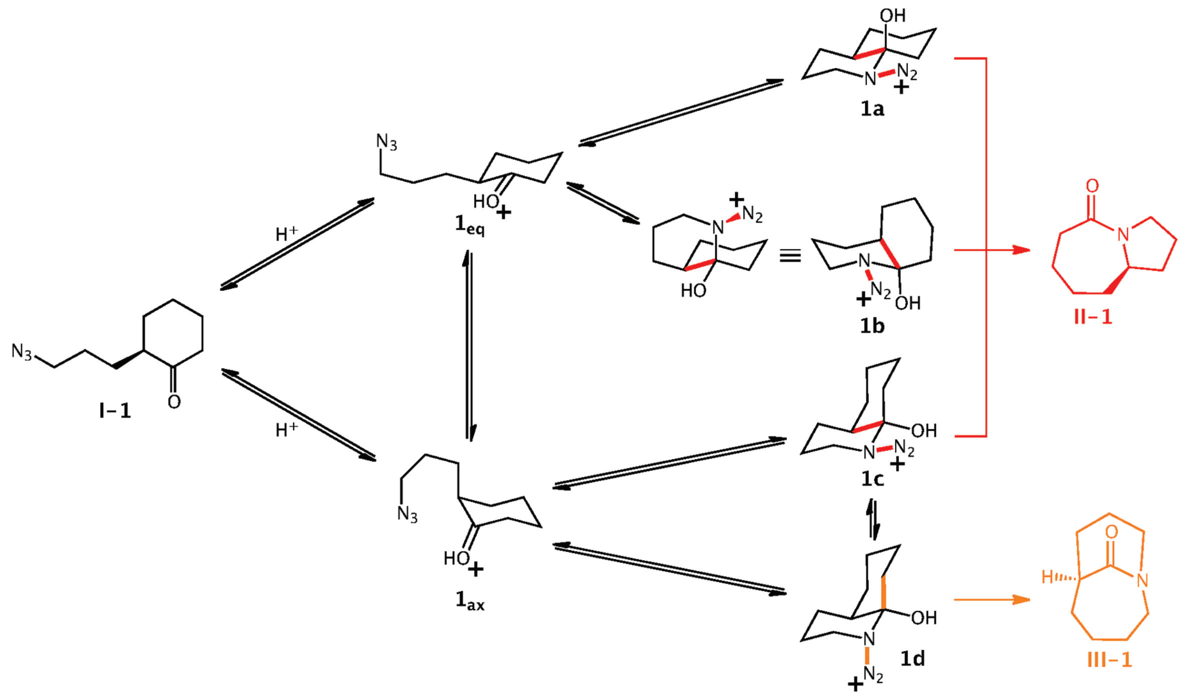
All structures were optimized using M06-2X[9] as implemented in GAUSSIAN09[10] with the 6-31G(d,p) basis set, along with treatment of solvation using the CPCM[11] solvation model (with UFF radii) unless otherwise noted. Experimentally, reactions were run in dichloromethane with various amounts (often excess) of various acids (usually TfOH, but also TFA and $HBF_4$).[1,2,4−6] It is not at all clear what dielectric constant is most appropriate to use in applying a continuum solvent model to such systems, but we settled on using a water model. Tests on several systems, including the parent ($R_1$=$R_2$=H) system (see the Supporting Information), with a dichloromethane continuum model indicated that the relative energies of competing transition state structures were not sensitive to the choice of solvent. In addition, energetics for the parent system were recalculated at the M06-2X/6-311++G(2d,2p)//M06-2X/6-311++G-(2d,2p) level, but no significant changes were found (vide infra). For all systems, several conformers with respect to rotation about C−OH, O/S−$CH_3$, and/or C−Ph bonds were evaluated, but only the lowest energy minima and transition state structures are discussed in detail herein; see the Supporting Information for information on others. For systems where sulfur−$N_2$ interactions were possible, long-range corrected B3LYP (CAM-B3LYP)[12] was also used used for comparison, even though M06-2X has been shown to be effective at treating a variety of noncovalent interactions.[13] For these systems, natural bond orbital (NBO) analysis[14] was used to assess the degree of lone pair−cation interactions. The B3LYP,[15] ωB97X-D,[16] and CAM-B3LYP[12] functionals were also used in some cases to assess the magnitudes of cation−π interactions. All stationary points were characterized as minima or transition state structures by frequency analysis. For representative transition state structures, intrinsic reaction coordinate (IRC) calculations[17] were performed to support putative connections between transition state structures and minima; see the Supporting Information for details.

## RESULTS AND DISCUSSION

**The Parent Reaction.** First, the intramolecular Schmidt reaction of the parent cyclohexanone **I** ($R_1$=$R_2$=H, Scheme 1) was examined. This system was shown to produce the fused lactam **II** exclusively (in 83% yield) upon treatment with trifluoroacetic acid (TFA).[2] In general, such reactions are thought to involve initial formation of azidohydrin intermediates (**1a−d**, Scheme 2), followed by loss of $N_2$ and migration of

**Received:** November 11, 2011
**Published:** November 29, 2011

Scheme 2



the C−C bond that is antiperiplanar (red or orange in Scheme 2) to the departing $N_2$ (these two events could occur sequentially, although they are generally thought to be coupled).[18] Assuming that an antiperiplanar arrangement of the migrating C−C bond and $N_2$ leaving group is required, intermediates **1a**−**c** will lead to fused lactam **II-1**, but intermediate **1d** will lead to bridged lactam **III-1** (Scheme 2). If rapid interconversion of intermediates **1a**−**d** (by reversion to $\mathbf{1}_{eq/ax}$, and/or nitrogen inversion for **1c**-to-**1d**) is assumed (i.e., Curtin−Hammett conditions[19]), then the transition state structure from **1d** to **III-1** should be higher in energy than at least one of the competing transition state structures to form **II-1**, because only **II-1** is observed for the $R_1$=$R_2$=H system.

Are these assumptions borne out by the results of our quantum chemical calculations? First, as shown in Figure 1, the four azidohydrin intermediates are predicted to lie within ~1 kcal/mol of each other in water. In addition, these intermediates are indeed predicted to interconvert rapidly through reversion to the ketoazide; $\mathbf{1}_{eq}$ and $\mathbf{1}_{ax}$ are predicted to be approximately 9 kcal/mol higher in energy than the intermediates, and the conversion from $\mathbf{1}_{eq}$/$\mathbf{1}_{ax}$ to the intermediates is predicted to be barrierless.[20] All attempts to find transition state structures for nitrogen inversion for **1c** and **1d** failed when using CPCM(water,UFF)-M06-2X/6-31G(d,p),[21] but such transition state structures were located with other theoretical methods (see the Supporting Information); barriers for inversion processes were predicted to be low (≤ approximately 2 kcal/mol) with these methods. Consequently, it seems that **1c** and **1d** can interconvert by nitrogen inversion, while **1a**−**d** can interconvert by reversion to the ketoazide ($\mathbf{1}_{eq}$/$\mathbf{1}_{ax}$).

The relative energies of the transition state structures connecting the intermediates to products span a slightly larger energy range than do the intermediate energies, however (Figure 1 and Table 1).[22] For example, transition state structure **1a-TS** is predicted to be 2 kcal/mol lower in free energy than **1d-TS**. Given that **1a-TS**, **1b-TS**, and **1c-TS** will yield the fused lactam

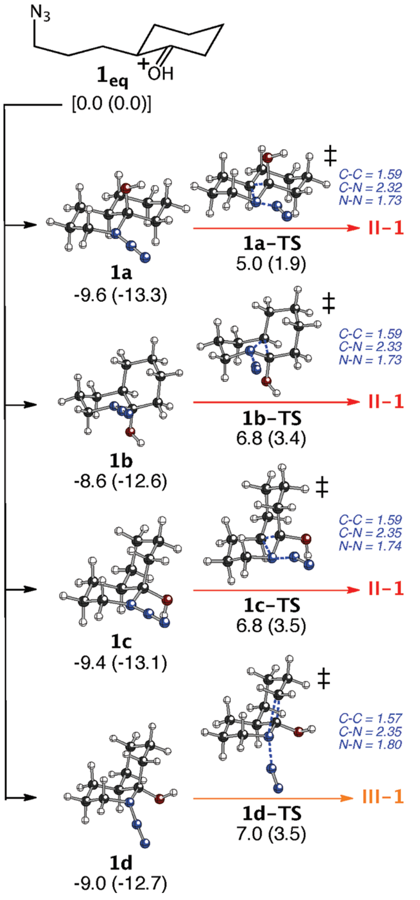


**Figure 1.** Relative free energies (kcal/mol at 298 K, relative to that of $\mathbf{1a}_{eq}$; enthalpies in parentheses; CPCM(water,UFF)-M06-2X/6-31G-(d,p)) for intermediates and 1,2-alkyl shift/$N_2$-loss transition state structures in the acid catalyzed Schmidt reaction of **I-1** (Scheme 2). Selected distances (blue) in Å.

Table 1. Relative Free Energies (kcal/mol; Enthalpies in Parentheses) for Intermediates and Transition State Structures Involved in the Acid-Promoted Schmidt Reactions of 1−8 and Product Ratios (Experimental and Calculated)[a]

| | | | | | | | fused/bridged | |
|---|---|---|---|---|---|---|---|---|
| system | R1 | R2 | intermediates | | transition state structures | | exp | calc |
| 1 | H | H | **1a** | 0.0 (0.0) | **1a-TS** | 14.6 (15.2) | >95:5 | 97:3 |
| | | | **1b** | 1.0 (0.7) | **1b-TS** | 16.4 (16.7) | | |
| | | | **1c** | 0.2 (0.2) | **1c-TS** | 16.4 (16.8) | | |
| | | | **1d** | 0.6 (0.6) | **1d-TS** | 16.6 (16.8) | | |
| 2 | *trans-t*-Bu | H | **2a** | 0.0 (0.0) | **2a-TS** | 14.6 (15.0) | 79:21 | 42:58 |
| | | | **2b** | 1.3 (1.1) | **2b-TS** | 16.9 (17.4) | | |
| | | | **2c** | −5.2 (−4.1) | **2c-TS** | 11.0 (12.4) | | |
| | | | **2d** | −4.6 (−3.5) | **2d-TS** | 10.8 (12.6) | | |
| 3 | *cis-t*-Bu | H | **3a** | 0.0 (0.0) | **3a-TS** | 14.7 (15.0) | >95:5 | only fused |
| | | | **3b** | 0.4 (0.5) | **3b-TS** | 16.2 (16.6) | | |
| | | | **3c** | 9.1 (8.1) | **3c-TS** | 25.4 (24.7) | | |
| | | | **3d** | 9.9 (8.7) | **3d-TS** | 25.7 (24.8) | | |
| 4 | H | SMe | **4a** | 0.0 (0.0) | **4a-TS** | 15.3 (15.5) | 20:80 | 13:87 (30:70) |
| | | | **4b** | 0.3 (0.0) | **4b-TS** | 16.6 (16.7) | | |
| | | | **4c** | −2.3 (−2.2) | **4c-TS** | 15.4 (15.6) | | |
| | | | **4d** | −1.2 (−1.8) | **4d-TS** | 13.8 (13.7) | | |
| 5 | H | OMe | **5a** | 0.0 (0.0) | **5a-TS** | 16.1 (16.4) | 68:32 | 31:69 (81:19) |
| | | | **5b** | 2.9 (3.0) | **5b-TS** | 15.5 (16.0) | | |
| | | | **5c** | −2.6 (−2.7) | **5c-TS** | 15.6 (15.9) | | |
| | | | **5d** | 0.5 (1.5) | **5d-TS** | 14.6 (15.6) | | |
| 6 | *trans-t*-Bu | SMe | **6c** | 0.0 (0.0) | **6c-TS** | 17.6 (17.7) | 14:86 | 12:86 (1:99) |
| | | | **6d** | 0.9 (0.2) | **6d-TS** | 16.4 (15.9) | | |
| 7 | H | Ph | **7a** | 0.0 (0.0) | **7a-TS** | 14.6 (15.0) | >95:5 | 85:15 |
| | | | **7b** | 0.1 (−0.3) | **7b-TS** | 15.8 (16.0) | | |
| | | | **7c** | 1.9 (1.5) | **7c-TS** | 15.8 (15.1) | | |
| | | | **7d** | 0.7 (0.4) | **7d-TS** | 15.5 (15.8) | | |
| 8 | *trans-t*-Bu | Ph | **8c** | 0.0 (0.0) | **8c-TS** | 17.7 (17.5) | 37:63 | 30:70 |
| | | | **8d** | 2.7 (1.9) | **8d-TS** | 17.2 (16.7) | | |

[a] All energies for each system are relative to that for intermediate **a** (for **1**−**5** and **7**) and **c** (for **6** and **8**). All structures were optimized at the CPCM(water,UFF)-M06-2X/6-31g(d,p) level. Calculated ratios are derived from Boltzmann distributions based on relative free energies of transition state structures. Calculated ratios in parentheses are based on the free energies of transition state structures complexed to one explicit water molecule (see text for discussion).

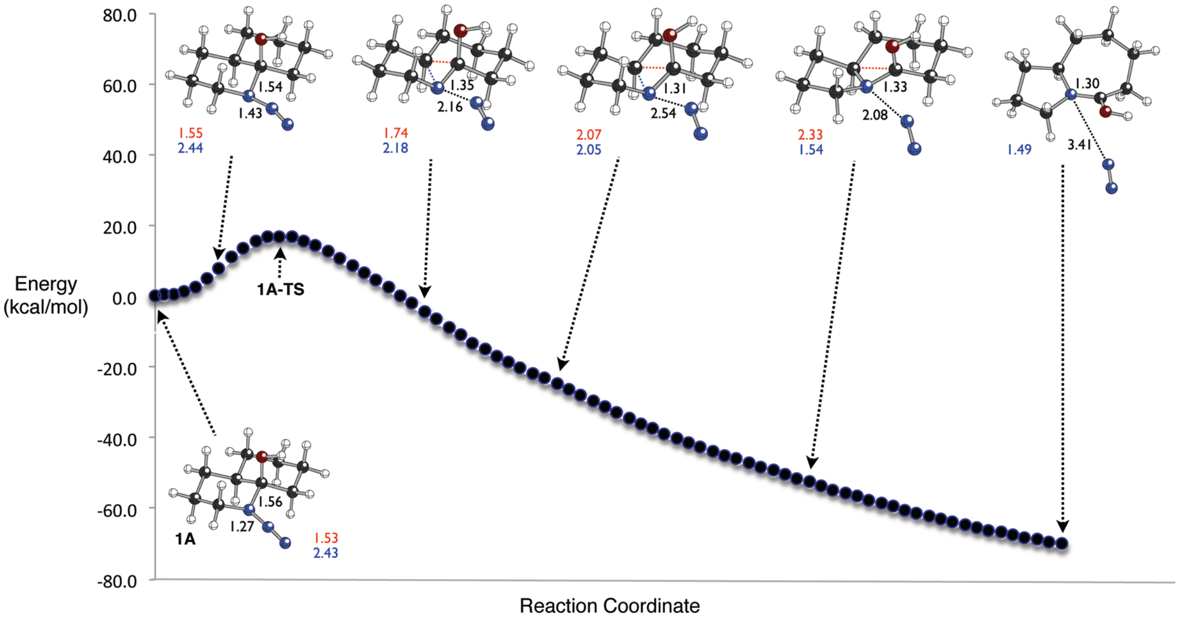
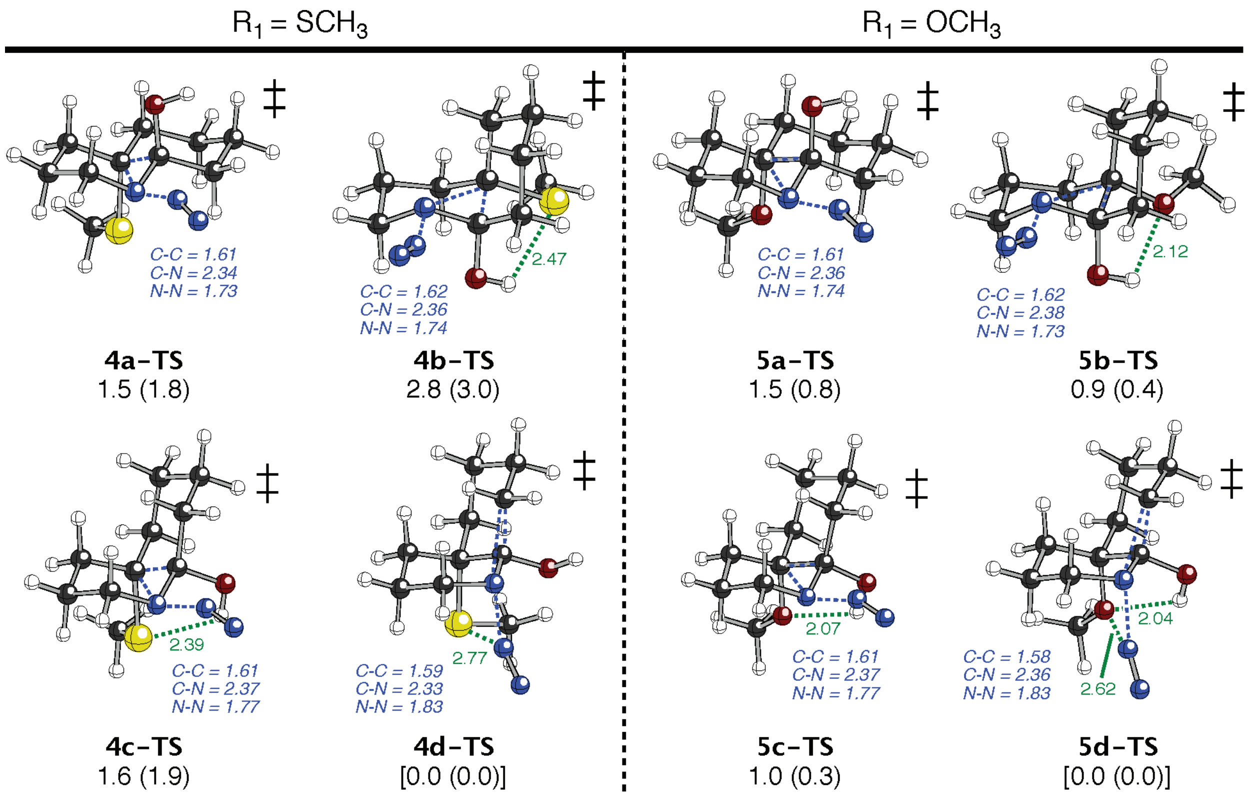


**Figure 2.** IRC plot for **1a-TS** (CPCM(water,UFF)-M06-2X/6-31G(d,p)). Selected distances are shown in Å. Blue numbers correspond to N−C distances for the forming bond and red numbers correspond to C−C distances for the breaking bond.



**4a–TS** 1.5 (1.8)

**4b–TS** 2.8 (3.0)

**5a–TS** 1.5 (0.8)

**5b–TS** 0.9 (0.4)

**4c–TS** 1.6 (1.9)

**4d–TS** [0.0 (0.0)]

**5c–TS** 1.0 (0.3)

**5d–TS** [0.0 (0.0)]

**Figure 3.** Relative free energies (kcal/mol at 298 K, relative to that of **1a**$_{\mathbf{eq}}$; enthalpies in parentheses; CPCM(water,UFF)-M06-2X/6-31G(d,p)) for 1,2-alkyl shift/$N_2$-loss transition state structures in the acid catalyzed Schmidt reaction of **I-4** ($R_2$=$SCH_3$) and **I-5** ($R_2$=$OCH_3$). Only the lowest energy conformation for each transition state structure is shown. Selected distances (blue and green) are shown in Å.

whereas **1d-TS** will lead to the bridged product, a Boltzmann distribution (at 298.15 K) taking into account the relative free energies of these four transition state structures leads to the prediction that a 97:3 fused/bridged product ratio should be expected (calculations using M06-2X/6-311++G(2d,2p) predicted essentially the same ratio).[23] This prediction agrees with the experimental ratio of >95:5.[2] The larger difference in energies between **1a-TS** and the other transition state structures compared to that for the corresponding intermediates is likely associated with increased 1,3-diaxial interactions between $CH_2$ groups of the azidoalkyl chains and the nearest $CH_2$ groups of the cyclohexanol ring in the higher energy transition state structures. For example, the closest contact shortens from 2.23 Å in **1d** to 2.13 Å in **1d-TS**. The *trans*-decalin relationship of the two rings in **1a** and **1a-TS** precludes such interactions.

Transformation of each intermediate to the corresponding protonated product is a concerted process, with $N_2$ departure slightly leading alkyl shifting (e.g., Figure 2). The transition state structures for these processes are early in terms of both events, consistent with the transformations being very exergonic, although the ring nitrogens are significantly more pyramidal in the transition state structures than in the azidohydrin intermediates (e.g., the sum of the angles around nitrogen for intermediate **1a** is 352°, whereas for **1a-TS** it is 325°).

**Conformationally Constrained Systems.** As expected, placing a *tert*-butyl group at the 4-position of the cyclohexanone ring was effective at reducing the number of productive conformers from four to two by disfavoring those in which the *tert*-butyl group would be axial (Table 1, systems 2 and 3).[5] When the *tert*-butyl group is positioned trans to the azidoalkyl chain, the **2a** and **2b** intermediate conformers and associated transition state structures (**2a-TS** and **2b-TS**) are predicted to be 3–7 kcal/mol higher in energy than the **2c** and **2d** conformers and transition state structures, respectively, because the *tert*-butyl groups in the former are in axial positions. Consequently, passage through **2c-TS** is the dominant route to fused product for this system. But, as for the parent system, the energy difference between **2c-TS** and **2d-TS** is predicted to be very small (here, $\Delta\Delta G^{\ddagger} = -0.2$ and $\Delta\Delta H^{\ddagger} = 0.2$). Experimentally, significant amounts of both fused (from **2c-TS**) and bridged (from **2d-TS**) lactams were produced.[5,24] When the *tert*-butyl group is positioned cis to the azidoalkyl chain, the **3c** and **3d** conformers and transition state structures are predicted to be 8–11 kcal/mol higher in energy than the **3a** and **3b** structures, because of severe steric clashes between the azidoalkyl and *tert*-butyl groups (see the Supporting Information for geometries). Consequently, formation of only the fused lactam product is predicted, consistent with what is observed experimentally.[2]

**Electron-Rich Substituents.** It was reasoned previously that installing a group capable of participating in lone pair–cation interactions, such as an ether or thioether, at the $R_2$ position (Scheme 1) would lead to preferential stabilization of intermediate **d** and the transition state structure following it, because the $R_2$ substituent and the cationic diazonium group would have a 1,3-diaxial relationship.[6,8] Since this transition state structure would lead to the bridged product, it was hoped that the use of ether or thioether substitutents would shift the product distribution toward bridged lactams. As discussed above, the ring nitrogen is predicted to be more pyramidal in the transition state structure than in the intermediate, so any selective stabilization should be more pronounced for the transition state structures.

Our calculations predict (see Table 1) that inclusion of a $SCH_3$ group at the $R_2$ position (Table 1, system 4) is indeed sufficient to reverse the fused/bridged preference, consistent

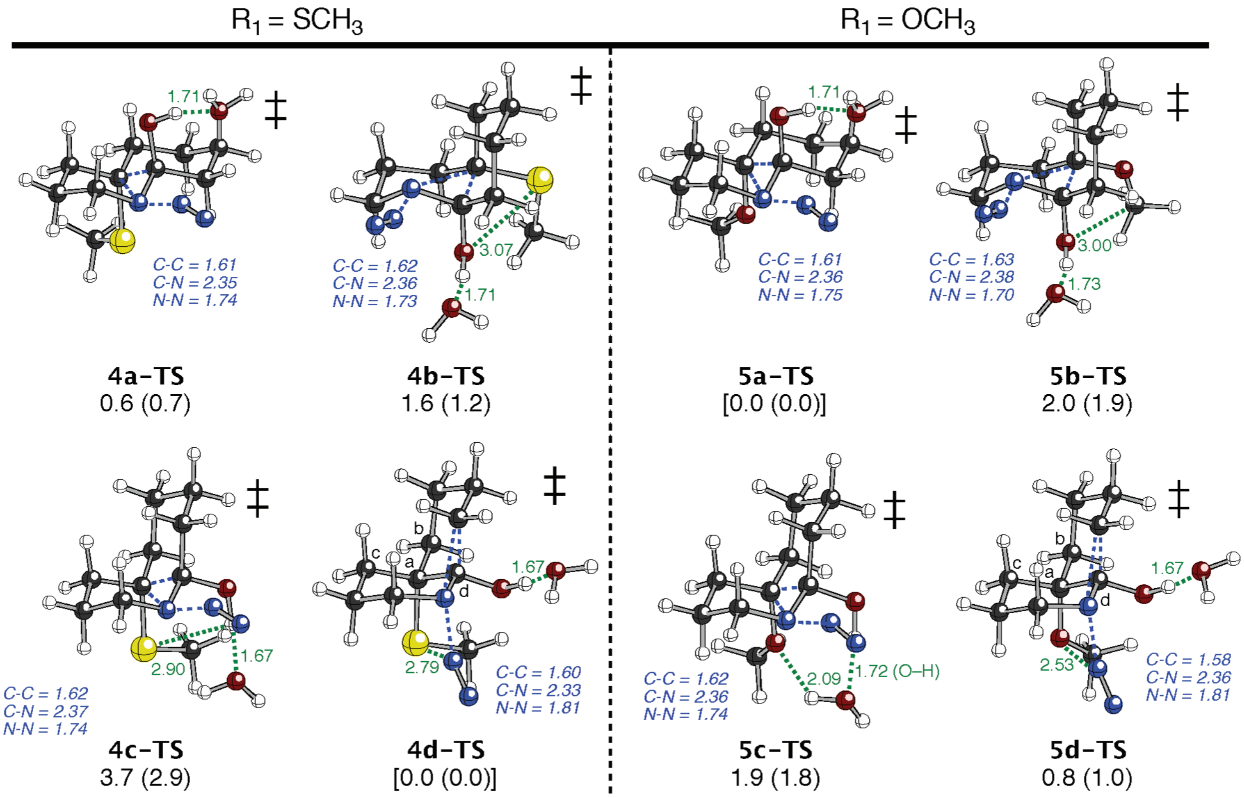


**Figure 4.** Relative free energies (kcal/mol at 298 K, relative to that of $\mathbf{1a_{eq}}$; enthalpies in parentheses; CPCM(water,UFF)-M06-2X/6-31G(d,p)) for 1,2-alkyl shift/$N_2$-loss transition state structures in the acid catalyzed Schmidt reaction of **I-4** ($R_2$=$SCH_3$) and **I-5** ($R_2$=$OCH_3$) with one explicit water molecule included. Only the lowest energy conformation for each transition state structure is shown. Selected distances (blue and green) are shown in Å. Note that in **4a-TS** and **5a-TS**, the water molecule blocks the view of one axial C–H bond.

with experimental results (notice that the selectivity predicted by intermediate energies would not be consistent with the experimental results).[6] In **4d-TS** (Figure 3), the S atom and $N_2$ leaving group are only 2.77 Å apart, and the central N atom of the $N_3$ unit is bent toward the S atom, consistent with a favorable interaction between these groups.[25] Experimentally, installing a methoxy group at the $R_2$ position (Table 1, system 5), however, did not lead to a predominance of the bridged product (68:32 ratio; Table 1).[6,26] This result was surprising, given the assumption that the lone pairs of the methoxy oxygen could also participate in interactions with the cationic diazonium group.[8] Along these lines, our calculations predict that the **5d-TS** transition state structure is actually lowest in energy, and consequently, we predict a 32:68 ratio of fused to bridged lactams, the opposite of the experimentally observed ratio.[27] As shown in Figure 3, the lowest energy transition state for both the thioether and methoxy systems is the **d-TS**, but the $XCH_3$ conformation is different for each. While both lowest energy transition state structures appear to have a lone pair–cation interaction, **5d-TS** appears also to have an intramolecular hydrogen bond not present in the lowest energy conformation of **4d-TS**. Given that such a hydrogen bond is less likely in the environment of the experiments (generally, TfOH in $CH_2Cl_2$), we decided to examine the effect of including an explicit water molecule (a crude model of TfOH and $TfO^-$) or an explicit $CH_2Cl_2$ molecule in the calculations (water-complexed systems are shown in Figure 4; $CH_2Cl_2$-complexed systems can be found in the Supporting Information). Upon including a water molecule, the predicted ratio did not change much for the thioether (30:70), but the product preference was indeed reversed for the methoxy-substituted system (81:19), now in reasonable agreement with the experimental ratio. Upon complexation, transition state structure **5a-TS** became the lowest in energy, and the conformation of **5d-TS** with the intramolecular hydrogen bond was predicted to be ~5 kcal/mol higher in energy (see the Supporting Information).[28]

What is the origin of this reversal of selectivity? To address this issue, we performed NBO analysis on **4d-TS** and **5d-TS** (Figure 4) to attempt to quantify the magnitude of interactions involving the S and O lone pairs. As shown in Table 2, hyperconjugation involving O lone pairs and nearby C–C bonds (present in all transition state structures) is predicted to be stronger than that involving S lone pairs (likely because of the better orbital overlap associated with O and C being in the same period), but the lone-pair cation ($\pi^*_{N-N}$) interaction is

**Table 2. NBO Analysis for $SCH_3$ (4d-TS) and $OCH_3$ (5d-TS) Substituted Transition State Structures (Figure 4) (CPCM(water,UFF)-M06-2X/6-31G(d,p))[a]**

| | 4d-TS | 5d-TS |
|---|---|---|
| $n_{S/O} \leftrightarrow \sigma^*_{C_a-C_b}$ | 3.6 | 7.2 |
| $n_{S/O} \leftrightarrow \sigma^*_{C_a-C_c}$ | 0.0[b] | 2.7 |
| $n_{S/O} \leftrightarrow \sigma^*_{C_a-C_d}$ | 7.1 | 10.8 |
| $n_{S/O} \leftrightarrow \pi^*_{N-N}$ | 9.5 | 4.0 |

[a] All energies are reported in kcal/mol. a–d atom labels are shown in Figure 4. [b] Threshold is 0.5 kcal/mol.

predicted to be stronger with S than with O.[29] This effect is counterbalanced somewhat by decreased steric interactions in **4a-TS** compared to **5a-TS** due to the longer C−$XCH_3$ bond with X=S.

As expected, when a *tert*-butyl group is appended to the cyclohexanone system (system 6; Table 1) there is still a preference for the bridged product.[6] In this case, calculations with an explicit water molecule overestimate the preference for the bridged product.

Replacing the $XCH_3$ groups in systems 4 and 5 (Table 1) with XH groups is predicted to lead to an interesting change in product selectivity. Although making such a change might be expected to promote the formation of fused products because steric problems for the **a-TS** transition state structures would be reduced, it actually is predicted to promote the formation of bridged products, even for the X=O system (the XH analogues of **4d-TS** and **5d-TS** are predicted to be 1.3 and 1.7 kcal/mol lower in energy than the XH analogues of **4a-TS** and **5a-TS**). Changing from $XCH_3$ to XH has two important consequences that may selectively favor the **d-TS** transition state structures. First, additional hydrogen bonds are introduced for **4d-TS** and **5d-TS** (Figure 5) but not for **4a-TS** and **5a-TS**. Second, these hydrogen bonds are expected to increase the electron density on X, thereby increasing the strength of the lone pair−cation interactions. The first of these clearly contributes, but the role of the second is unclear, since X−N distances actually increase upon changing from $XCH_3$ to XH, hinting that the new hydrogen bonding interactions may take precedence over the lone pair−cation interactions. The predicted change in selectivity awaits experimental verification.

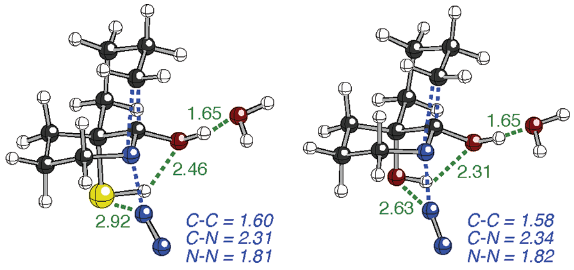


**Figure 5.** Computed structures for XH analogues of **4d-TS** and **5d-TS** complexed to water (CPCM(water,UFF)-M06-2X/6-31G(d,p)). Selected distances (blue and green) are shown in Å.

**Aryl Substitutents.** As shown in Table 1, including a phenyl group (system 7), which could provide selective transition state stabilization through a cation−$\pi$ interaction,[7] at the $R_2$ position is by itself not enough to change the preference for fused product (experimentally observed and predicted).[5,6] Note, however, that this preference is predicted to be less for system 7 than for system 1, indicating that the phenyl group does have an effect. For system 8, **8c-TS** and **8d-TS** are predicted to be very close in energy (Table 1), implying that conformationally locking the system into these two forms should lead to a mixture of fused and bridged product, which is observed experimentally.[5]

Is the effect of the phenyl group actually the result of a cation−$\pi$ interaction? As shown in Figure 6, the phenyl ring in **7d-TS** does prefer to orient itself so as to face the $N_2$ leaving group, even though this increases steric effects with one $CH_2$ group. Furthermore, the distance from the center of the phenyl ring to the $N_2$ group is 3.20 Å, which is well within the range of typical cation−$\pi$ interactions.[30]

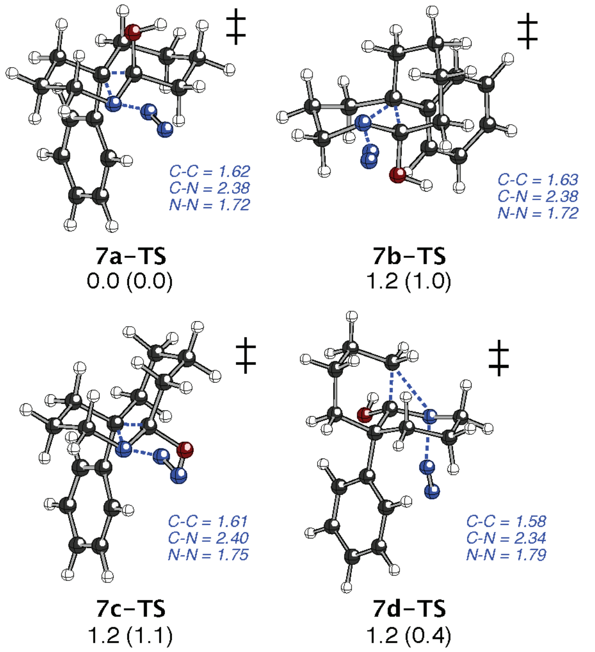
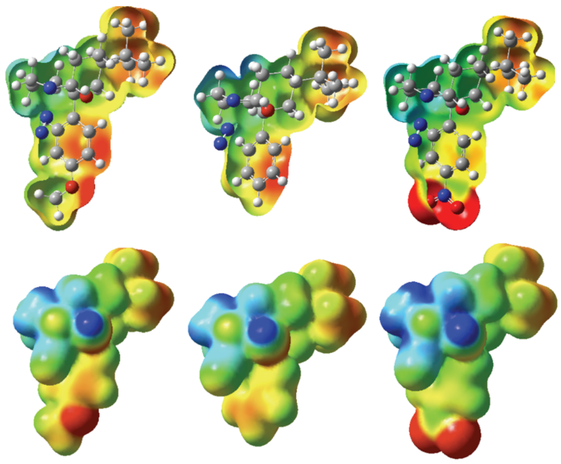


**Figure 6.** Relative free energies (kcal/mol; 298 K; enthalpies in parentheses) for the acid-catalyzed intramolecular Schimdt reaction of $\alpha$-substituted methyl thioether ketones. Structures were optimized using M06-2X/6-31G(d,p) in water (CPCM;UFF). Only the lowest energy conformers are shown. Note that the **7d-TS** structure is viewed from a different angle than in previous figures.



| | 8d-TS-OMe | 8d-TS | 8d-TS-$NO_2$ |
|---|---|---|---|
| *M06-2X* | -0.8 (3.04 Å) | -0.4 (3.20 Å) | -0.7 (3.34 Å) |
| *M06-2X*[(a)] | -0.8 (3.02 Å) | -0.3 (3.18 Å) | -0.7 (3.33 Å) |
| *M06-2X*[(b)] | -1.1 (3.14 Å) | -0.4 (3.25 Å) | -0.8 (3.35 Å) |
| *B3LYP* | -1.1 (3.01 Å) | 1.5 (3.27 Å) | 0.6 (3.50 Å) |
| *CAM-B3LYP* | -0.1 (3.15 Å) | 0.2 (3.33 Å) | -0.1 (3.46 Å) |
| *ωB97X-D* | -1.2 (3.05 Å) | 0.1 (3.26 Å) | -0.7 (3.37 Å) |

**Figure 7.** Electrostatic potential maps (isovalue = 0.007; 0.07 (red, most negative) to 0.25 (blue, least negative)) for transition state structures **8d-TS**-OMe/**8d-Ts**/**8d-TS**-NO2 and predicted free energy differences (kcal/mol) between the **d-TS** and **c-TS** transition state structures optimized with different methods (all with CPCM-(water,UFF) and the 6-31G(d,p) basis set except for (a) optimized using CPCM($CH_2Cl_2$,UFF) and (b) optimized using the 6-311+G(d,p) basis set).

As an additional probe, representative electron-donating ($OCH_3$) and -withdrawing ($NO_2$) groups were added to the para position of the aromatic ring for system 8 (the *tert*-butyl-containing analogue of system 7, Table 1), and the energy differences between the **c-TS** and **d-TS** transition state structures were evaluated at various levels of theory (Figure 7, bottom; see the Methods section for details). Among the functionals examined, only M06-2X predicts that the bridged product is favored for both Ph and *para*-$OCH_3$−Ph systems, an effect observed experimentally when promoting these reactions with a Lewis acid.[31] Overall, all methods predicted only a small substituent effect on product selectivity and no significant decrease in preference for bridged product upon switching from *para*-$OCH_3$ to *para*-$NO_2$. Experimentally, using a Lewis acid catalyst led to a roughly equal mixture of fused and bridged products.[31] All methods predicted, however, an increase in the distance between the center of the phenyl ring and the $N_2$ group as the aryl group changes from *para*-$OCH_3$−Ph to Ph to *para*-$NO_2$−Ph. In addition, although the effect is subtle, the $N_2$ group appears to be most positively charged for the *para*-$NO_2$−Ph substituted system (see Figure 7, top, for electrostatic potential maps).[32]

## ■ CONCLUSIONS

The results of quantum chemical calculations on acid-promoted intramolecular Schmidt reactions of azidopropylcyclohexanones indicate that these reactions involve rapid and reversible formation of azidohydrin intermediates followed by concerted $N_2$-loss and shifting of the alkyl group that is antiperiplanar to the $N_2$ leaving group. The M06-2X functional was found to predict product ratios for these reactions that generally agree with experimentally determined ratios. The roles of steric effects, lone pair−cation and cation−$\pi$ interactions on the fused/bridged product selectivity have been confirmed, characterized theoretically and quantified. While other explanations for the effects described herein may be possible, the reactivity models we describe are consistent with the experimental results and have predictive value.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Additional details on computations, including energies and coordinates for all minima and transition state structures, IRC plots, and full GAUSSIAN reference. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: tantillo@chem.ucdavis.edu.

## ■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Institutes of General Medical Sciences (GM49093) and the National Science Foundation (CHE030089 through Pittsburgh Supercomputer Center), Robert M. Husing and Mindy and Lyle Defenbaugh for support, and Ruzhang Liu and Michal Szostak for helpful comments.

## ■ REFERENCES

(1) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965−8966.

(2) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449−10459.

(3) Selected examples of studies on bridged bicyclic lactams: (a) Coqueret, X.; Bourellewargnier, F.; Chuche, J. *J. Org. Chem.* **1985**, *50*, 909−910. (b) Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697−1699. (c) Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073−1081. (d) Lease, T. G.; Shea, K. J. *J. Am. Chem. Soc.* **1993**, *115*, 2248−2260. (e) Kirby, A. J.; Komarov, I. V.; Feeder, N. *J. Chem. Soc., Perkin Trans. 2* **2001**, 522−529. (f) Bashore, C. G.; Samardjiev, I. J.; Bordner, J.; Coe, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 3268−3272. (g) Tani, K.; Stoltz, B. M. *Nature* **2006**, *441*, 731−734, (in this report, an intramolecular Schmidt reaction of a $\beta$-azidoalkylketone, rather than $\alpha$-azidoalkylketone, was utilized). (h) Ribelin, T. P.; Judd, A. S.; Akritopoulou-Zanze, I.; Henry, R. F.; Cross, J. L.; Whittern, D. N.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 5119−5122.

(4) Yao, L.; Aubé, J. *J. Am. Chem. Soc.* **2007**, *129*, 2766−2767.

(5) Szostak, M.; Yao, L.; Aubé, J. *J. Org. Chem.* **2009**, *74*, 1869−1875.

(6) Szostak, M.; Yao, L.; Aubé, J. *Org. Lett.* **2009**, *11*, 4386−4389.

(7) For leading references, see: (a) Dougherty, D. *Science* **1996**, *271*, 163−168. (b) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303−1324.

(8) Related theoretical work: (a) Ribelin, T.; Katz, C. E.; English, D.; Smith, S.; Manukyan, A. K.; Day, V. W.; Neuenswander, B.; Poutsma, J. L.; Aubé, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6233−6235. (b) Katz, C. E.; Ribelin, T.; Withrow, D.; Basser, Y.; Manukyan, A. K.; Bermudez, A.; Nuera, C. G.; Day, V. W.; Powell, D. R.; Poutsma, J. L.; Aubé, J. *J. Org. Chem.* **2008**, *73*, 3318−3327. (c) Hewlett, N. D.; Aubé, J.; Radkiewicz-Poutsma, J. L. *J. Org. Chem.* **2004**, *69*, 3429−3446. (d) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W. K.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183−10194.

(9) Zhao, Y.; Thrular, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241.

(10) Frish, M. J.; et al. *GAUSSIAN09*, Revision A.02; Gaussian, Inc.: Wallingford CT, 2009. Full citation in Supporting Information.

(11) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995−2001.

(12) Yanai, T.; Tew, D.; Handy, N. *Chem. Phys. Lett.* **2004**, *293*, 51−57.

(13) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157−167.

(14) (a) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1998**, *88*, 899−926. (b) For a representative paper in which NBO was used to analyze noncovalent interactions in Se···O systems, see: Iwaoka, M; Komatsu, H.; Katsuda, T.; Tomoda, S. *J. Am. Chem. Soc.* **2004**, *126*, 5309−5317.

(15) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372−1377. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785−789. (d) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627.

(16) Chai, J.-D.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615−6620.

(17) (a) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523−5527. (b) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363−368.

(18) For reviews on the Schmidt reaction, see: (a) Wolff, H. *Org. React.* **1946**, *3*, 307−336. (b) Uyeo, S. *Pure Appl. Chem.* **1963**, *7*, 269−283. (c) Smith, P. A. S. In *Molecular Rearrangements*; de Mayo, P., Ed.; John Wiley & Sons: New York, 1963; Vol *1*, pp 457−591. (d) Banthorpe, D. V. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley & Sons: London, 1971; pp 397−440. (e) Abramovich, R. A.; Kyba, E. P. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley & Sons: London, 1971; pp 221−329. (f) Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279−1300. (g) Kow, G. R. *Tetrahedron* **1981**, *37*, 1283−1307. (h) Kyba, E. P. In *Azides and Nitrenes I: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: Orlando, FL, 1984; pp 2−34.

(19) (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 110−128. (b) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134. (c) Seeman, J. I. *J. Chem. Educ.* **1986**, *63*, 42−48. (d) Haupert, L. J.; Poutsma, J. C.; Wenthold, P. G. *Acc. Chem. Res.* **2009**, *42*, 1480−1488.

(20) Some methods predict a very small barrier leading to the intermediates; see the Supporting Information for further details.

(21) As shown in Figure 1, **1c** and **1d** differ in both the orientation of the N−$N_2$ group (occupying a pseudoaxial or pseudoequatorial position) and the orientation of the O−H bond ("down" as in **1c** or

"up" as in **1d**). All attempts to find an intermediate with the same O−H orientation but different $N-N_2$ orientation (e.g., O−H "up" with pseudoequatorial $N-N_2$ or O−H "down" with pseudoaxial $N-N_2$) failed and instead converged back to either **1c** or **1d** using this methodology.

(22) Similar results were obtained at other levels of theory; see the Supporting Information for details.

(23) Calculations (CPCM(water,UFF)-B3LYP/6-31G(d,p)-SDD) using $SnCl_4$ (a common Lewis acid also used to promote these reactions) in place of the OH proton predicted a very similar regioselectivity preference (98:2), suggesting that direct interactions between the Lewis acid and the bicycle do contribute significantly to selectivity. Also, calculations on these systems in DCM predicted the same product distribution. See the Supporting Information for further details.

(24) The fused/bridge ratio for this system was sensitive to the reaction conditions used, although the fused was the major product in all cases.[5] While the predicted and observed ratios may differ as a result of approximations in the calculations, it is also possible that the bridged product decomposes selectively for this system.

(25) Calculations with CAM-B3LYP, a functional designed to treat dispersion interactions, led to similar results. See the Supporting Information for details.

(26) Here, the experimental ratio includes elimination products arising from the fused lactam.

(27) A similar ratio was predicted when a larger basis set (6-311+G(d,p)) was used; see the Supporting Information.

(28) (a) Calculations with two water molecules (one hydrogen bonded to the OH and the other to the ether/thioether) led to similar predicted relative energies. The energy difference between **5a-TS** and **5d-TS** was predicted to be 1.3 kcal/mol (versus 0.8 kcal/mol with one water molecule), favoring the fused product, and the energy difference between **4a-TS** and **4d-TS** was predicted to be 0.4 kcal/mol (versus 0.6 kcal/mol with one water molecule), favoring the bridged product. (b) Aside from the calculations described above that made use of explicit water and dichloromethane molecules, no other treatment of explicit reactant−Lewis base interactions was attempted. (c) See also ref 5 for a related discussion on the effects of excess Lewis acids.

(29) Sulfur lone pairs are expected to be better donors than oxygen lone pairs; see: Kimura, J. E.; Szent-Györgyi, A. *Proc. Natl. Acad. Sci. U. S. A.* **1969**, *62*, 286−288.

(30) Gallivan, J. P.; Dougherty, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 870−874.

(31) Experimental ratios for these systems were determined using $CH_3AlCl_2$ in dichloromethane.[4] Additional calculations are underway to examine the effects of Lewis acids on the product selectivity.

(32) For cautions regarding the use of electrostatic potential maps to assess the origins of substitutent effects on cation−$\pi$ interactions, see: Wheeler, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 10262−10274. Wheeler, S. E.; Houk, K. N. *J. Chem. Theory Comput.* **2009**, *5*, 2301−2312.